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tent).

Published

With international search report.

(54) Title: OSTEOGENIC DEVICES

(57) Abstract

Disclosed are 1) amino acid sequence data, structural features, and various other data characterizing a human os protein, OPI, 2) osteogenic devices comprising a heat treated xenogenic bone collagen matrix containing osteogenic pr methods of producing osteogenic proteins using recombinant DNA technology and 4) use of osteogenic devices to mimic ural course of endochondral bone formation in mammals.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Oppermann, Hermann
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Pang, Roy H.L.
- (ii) TITLE OF INVENTION: Osteogenic Devices
- (iii) NUMBER OF SEQUENCE: 7
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Lahive & Cockfield
 - (B) STREET: 60 State Street
 - (C) CITY: Boston
 - (D) STATE: Massachusetts
 - (E) COUNTRY: U.S.A.
 - (F) ZIP: 02109
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Diskette, 3.5 inch,
720kb storage
 - (B) COMPUTER: IBM XT
 - (C) OPERATING SYSTEM: DOS 3.30
 - (D) SOFTWARE: Word Perfect 5.0
- (vi) CURRENT APPLICATION DATA:
 - (B) FILING DATE: 20-Aug-90
- (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: US 422,699
 - (B) FILING DATE: 17-Oct-89
 - (C) APPLICATION NUMBER: US 483,913
 - (D) FILING DATE: 22-Feb-89

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 139 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Ser	Thr	Gly	Ser	Lys	Gln	Arg	Ser	Gln
1				5				
Asn	Arg	Ser	Lys	Thr	Pro	Lys	Asn	Gln
10					15			
Glu	Ala	Leu	Arg	Met	Ala	Asn	Val	Ala
20						25		
Glu	Asn	Ser	Ser	Ser	Asp	Gln	Arg	Gln
		30					35	
Ala	Cys	Lys	Lys	His	Glu	Leu	Tyr	Val
			40					45
Ser	Phe	Arg	Asp	Leu	Gly	Trp	Gln	Asp
				50				
Trp	Ile	Ile	Ala	Pro	Glu	Gly	Tyr	Ala
55					60			
Ala	Tyr	Tyr	Cys	Glu	Gly	Glu	Cys	Ala
	65					70		
Phe	Pro	Leu	Asn	Ser	Tyr	Met	Asn	Ala
		75					80	
Thr	Asn	His	Ala	Ile	Val	Gln	Thr	Leu
			85					90
Val	His	Phe	Ile	Asn	Pro	Glu	Thr	Val
				95				
Pro	Lys	Pro	Cys	Cys	Ala	Pro	Thr	Gln
100					105			
Leu	Asn	Ala	Ile	Ser	Val	Leu	Tyr	Phe
	110					115		

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Asp	Asp	Ser	Ser	Asn	Val	Ile	Leu	Lys
		120					125	
Lys	Tyr	Arg	Asn	Met	Val	Val	Arg	Ala
			130					135
Cys	Gly	Cys	His					

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 132 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

							Ser	Gln
							1	
Asn	Arg	Ser	Lys	Thr	Pro	Lys	Asn	Gln
		5					10	
Glu	Ala	Leu	Arg	Met	Ala	Asn	Val	Ala
			15					20
Glu	Asn	Ser	Ser	Ser	Asp	Gln	Arg	Gln
				25				
Ala	Cys	Lys	Lys	His	Glu	Leu	Tyr	Val
30					35			
Ser	Phe	Arg	Asp	Leu	Gly	Trp	Gln	Asp
	40					45		
Trp	Ile	Ile	Ala	Pro	Glu	Gly	Tyr	Ala
		50					55	
Ala	Tyr	Tyr	Cys	Glu	Gly	Glu	Cys	Ala
			60					65
Phe	Pro	Leu	Asn	Ser	Tyr	Met	Asn	Ala
				70				

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Thr 75	Asn	His	Ala	Ile	Val 80	Gln	Thr	Leu
Val 85	His	Phe	Ile	Asn	Pro	Glu 90	Thr	Val
Pro	Lys	Pro 95	Cys	Cys	Ala	Pro	Thr 100	Gln
Leu	Asn	Ala	Ile 105	Ser	Val	Leu	Tyr	Phe 110
Asp	Asp	Ser	Ser	Asn 115	Val	Ile	Leu	Lys
Lys 120	Tyr	Arg	Asn	Met	Val 125	Val	Arg	Ala
Cys 130	Gly	Cys	His.					

(2) INFORMATION FOR SEQ ID NO:3:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 119 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Leu 1	Arg	Met	Ala	Asn 5	Val	Ala	Glu	Asn
Ser 10	Ser	Ser	Asp	Gln	Arg 15	Gln	Ala	Cys
Lys 20	Lys	His	Glu	Leu	Tyr	Val 25	Ser	Phe
Arg	Asp	Leu 30	Gly	Trp	Gln	Asp	Trp 35	Ile
Ile	Ala	Pro	Glu 40	Gly	Tyr	Ala	Ala	Tyr 45

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Tyr	Cys	Glu	Gly	Glu	Cys	Ala	Phe	Pro
				50				
Leu	Asn	Ser	Tyr	Met	Asn	Ala	Thr	Asn
55					60			
His	Ala	Ile	Val	Gln	Thr	Leu	Val	His
	65					70		
Phe	Ile	Asn	Pro	Glu	Thr	Val	Pro	Lys
		75					80	
Pro	Cys	Cys	Ala	Pro	Thr	Gln	Leu	Asn
			85					90
Ala	Ile	Ser	Val	Leu	Tyr	Phe	Asp	Asp
				95				
Ser	Ser	Asn	Val	Ile	Leu	Lys	Lys	Tyr
100					105			
Arg	Asn	Met	Val	Val	Arg	Ala	Cys	Gly
	110					115		
Cys	His							

(2) INFORMATION FOR SEQ ID NO:4:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 117 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

		Met	Ala	Asn	Val	Ala	Glu	Asn
		1				5		
Ser	Ser	Ser	Asp	Gln	Arg	Gln	Ala	Cys
		10					15	
Lys	Lys	His	Glu	Leu	Tyr	Val	Ser	Phe
			20					25
Arg	Asp	Leu	Gly	Trp	Gln	Asp	Trp	Ile
				30				

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Ile	Ala	Pro	Glu	Gly	Tyr	Ala	Ala	Tyr
35					40			
Tyr	Cys	Glu	Gly	Glu	Cys	Ala	Phe	Pro
	45					50		
Leu	Asn	Ser	Tyr	Met	Asn	Ala	Thr	Asn
		55					60	
His	Ala	Ile	Val	Gln	Thr	Leu	Val	His
			65					70
Phe	Ile	Asn	Pro	Glu	Thr	Val	Pro	Lys
				75				
Pro	Cys	Cys	Ala	Pro	Thr	Gln	Leu	Asn
80					85			
Ala	Ile	Ser	Val	Leu	Tyr	Phe	Asp	Asp
	90					95		
Ser	Ser	Asn	Val	Ile	Leu	Lys	Lys	Tyr
		100					105	
Arg	Asn	Met	Val	Val	Arg	Ala	Cys	Gly
			110					115
Cys	His							

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 116 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

			Ala	Asn	Val	Ala	Glu	Asn
			1				5	
Ser	Ser	Ser	Asp	Gln	Arg	Gln	Ala	Cys
			10					15
Lys	Lys	His	Glu	Leu	Tyr	Val	Ser	Phe
				20				

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Arg 25	Asp	Leu	Gly	Trp	Gln 30	Asp	Trp	Ile
Ile 35	Ala	Pro	Glu	Gly	Tyr	Ala 40	Ala	Tyr
Tyr	Cys	Glu 45	Gly	Glu	Cys	Ala	Phe 50	Pro
Leu	Asn	Ser	Tyr 55	Met	Asn	Ala	Thr	Asn 60
His	Ala	Ile	Val	Gln 65	Thr	Leu	Val	His
Phe 70	Ile	Asn	Pro	Glu	Thr 75	Val	Pro	Lys
Pro	Cys 80	Cys	Ala	Pro	Thr	Gln 85	Leu	Asn
Ala	Ile	Ser 90	Val	Leu	Tyr	Phe	Asp 95	Asp
Ser	Ser	Asn	Val 100	Ile	Leu	Lys	Lys	Tyr 105
Arg	Asn	Met	Val	Val 110	Arg	Ala	Cys	Gly
Cys 115	His	.						

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 114 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Val	Ala	Glu	Asn	Ser	Ser	Ser	Asp	Gln
1				5				
Arg	Gln	Ala	Cys	Lys	Lys	His	Glu	Leu
10					15			
Tyr	Val	Ser	Phe	Arg	Asp	Leu	Gly	Trp
	20					25		
Gln	Asp	Trp	Ile	Ile	Ala	Pro	Glu	Gly
		30					35	
Tyr	Ala	Ala	Tyr	Tyr	Cys	Glu	Gly	Glu
			40					45
Cys	Ala	Phe	Pro	Leu	Asn	Ser	Tyr	Met
				50				
Asn	Ala	Thr	Asn	His	Ala	Ile	Val	Gln
55					60			
Thr	Leu	Val	His	Phe	Ile	Asn	Pro	Glu
	65					70		
Thr	Val	Pro	Lys	Pro	Cys	Cys	Ala	Pro
		75					80	
Thr	Gln	Leu	Asn	Ala	Ile	Ser	Val	Leu
			85					90
Tyr	Phe	Asp	Asp	Ser	Ser	Asn	Val	Ile
				95				
Leu	Lys	Lys	Tyr	Arg	Asn	Met	Val	Val
100					105			
Arg	Ala	Cys	Gly	Cys	His			
	110							

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1822 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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- (ii) MOLECULE TYPE: cDNA to mRNA
- (iii) HYPOTHETICAL: no
- (iv) ANTI-SENSE: no
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: Bovinae
 - (F) TISSUE TYPE: bone
- (vii) IMMEDIATE SOURCE:
 - (A) LIBRARY: human placenta
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGTGCGGGCC CGGAGCCCGG AGCCCGGGTA GCGCGTAGAG	40
CCGGCGCG ATG CAC GTG CGC TCA CTG CGA GCT GCG	75
Met His Val Arg Ser Leu Arg Ala Ala	
1 5	
GCG CCG CAC AGC TTC GTG GCG CTC TGG GCA CCC	108
Ala Pro His Ser Phe Val Ala Leu Trp Ala Pro	
10 15 20	
CTG TTC CTG CTG CGC TCC GCC CTG GCC GAC TTC	141
Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe	
25 30	
AGC CTG GAC AAC GAG GTG CAC TCG AGC TTC ATC	174
Ser Leu Asp Asn Glu Val His Ser Ser Phe Ile	
35 40	
CAC CGG CGC CTC CGC AGC CAG GAG CGG CGG GAG	207
His Arg Arg Leu Arg Ser Gln Glu Arg Arg Glu	
45 50	
ATG CAG CGC GAG ATC CTC TCC ATT TTG GGC TTG	240
Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu	
55 60	
CCC CAC CGC CCG CGC CCG CAC CTC CAG GGC AAG	273
Pro His Arg Pro Arg Pro His Leu Gln Gly Lys	
65 70 75	

CAC AAC TCG GCA CCC ATG TTC ATG CTG GAC CTG 306
 His Asn Ser Ala Pro Met Phe Met Leu Asp Leu
 80 85

TAC AAC GCC ATG GCG GTG GAG GAG GGC GGC GGG 339
 Tyr Asn Ala Met Ala Val Glu Glu Gly Gly Gly
 90 95

CCC GGC GGC CAG GGC TTC TCC TAC CCC TAC AAG 372
 Pro Gly Gly Gln Gly Phe Ser Tyr Pro Tyr Lys
 100 105

GCC GTC TTC AGT ACC CAG GGC CCC CCT CTG GCC 405
 Ala Val Phe Ser Thr Gln Gly Pro Pro Leu Ala
 110 115

AGC CTG CAA GAT AGC CAT TTC CTC ACC GAC GCC 438
 Ser Leu Gln Asp Ser His Phe Leu Thr Asp Ala
 120 125 130

GAC ATG GTC ATG AGC TTC GTC AAC CTC GTG GAA 471
 Asp Met Val Met Ser Phe Val Asn Leu Val Glu
 135 140

CAT GAC AAG GAA TTC TTC CAC CCA CGC TAC CAC 504
 His Asp Lys Glu Phe Phe His Pro Arg Tyr His
 145 150

CAT CGA GAG TTC CGG TTT GAT CTT TCC AAG ATC 537
 His Arg Glu Phe Arg Phe Asp Leu Ser Lys Ile
 155 160

CCA GAA GGG GAA GCT GTC ACG GCA GCC GAA TTC 570
 Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe
 165 170

CGG ATC TAC AAG GAC TAC ATC CGG GAA CGC TTC 603
 Arg Ile Tyr Lys Asp Tyr Ile Arg Glu Arg Phe
 175 180 185

GAC AAT GAG ACG TTC CGG ATC AGC GTT TAT CAG 636
 Asp Asn Glu Thr Phe Arg Ile Ser Val Tyr Gln
 190 195

GTG CTC CAG GAG CAC TTG GGC AGG GAA TCG GAT 669

Val	Leu	Gln	Glu	His	Leu	Gly	Arg	Glu	Ser	Asp	
			200					205			
CTC	TTC	CTG	CTC	GAC	AGC	CGT	ACC	CTC	TGG	GCC	702
Leu	Phe	Leu	Leu	Asp	Ser	Arg	Thr	Leu	Trp	Ala	
		210					215				
TCG	GAG	GAG	GGC	TGG	CTG	GTG	TTT	GAC	ATC	ACA	735
Ser	Glu	Glu	Gly	Trp	Leu	Val	Phe	Asp	Ile	Thr	
		220				225					
GCC	ACC	AGC	AAC	CAC	TGG	GTG	GTC	AAT	CCG	CGG	768
Ala	Thr	Ser	Asn	His	Trp	Val	Val	Asn	Pro	Arg	
		230			235					240	
CAC	AAC	CTG	GGC	CTG	CAG	CTC	TCG	GTG	GAG	ACG	801
His	Asn	Leu	Gly	Leu	Gln	Leu	Ser	Val	Glu	Thr	
			245						250		
CTG	GAT	GGG	CAG	AGC	ATC	AAC	CCC	AAG	TTG	GCG	834
Leu	Asp	Gly	Gln	Ser	Ile	Asn	Pro	Lys	Leu	Ala	
			255					260			
GGC	CTG	ATT	GGG	CGG	CAC	GGG	CCC	CAG	AAC	AAG	867
Gly	Leu	Ile	Gly	Arg	His	Gly	Pro	Gln	Asn	Lys	
		265					270				
CAG	CCC	TTC	ATG	GTG	GCT	TTC	TTC	AAG	GCC	ACG	900
Gln	Pro	Phe	Met	Val	Ala	Phe	Phe	Lys	Ala	Thr	
		275				280					
GAG	GTC	CAC	TTC	CGC	AGC	ATC	CGG	TCC	ACG	GGG	933
Glu	Val	His	Phe	Arg	Ser	Ile	Arg	Ser	Thr	Gly	
		285				290				295	
AGC	AAA	CAG	CGC	AGC	CAG	AAC	CGC	TCC	AAG	ACG	966
Ser	Lys	Gln	Arg	Ser	Gln	Asn	Arg	Ser	Lys	Thr	
			300						305		
CCC	AAG	AAC	CAG	GAA	GCC	CTG	CGG	ATG	GCC	AAC	999
Pro	Lys	Asn	Gln	Glu	Ala	Leu	Arg	Met	Ala	Asn	
			310					315			
GTG	GCA	GAG	AAC	AGC	AGC	AGC	GAC	CAG	AGG	CAG	1032

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Val	Ala	Glu	Asn	Ser	Ser	Ser	Asp	Gln	Arg	Gln		
		320					325					
GCC	TGT	AAG	AAG	CAC	GAG	CTG	TAT	GTC	AGC	TTC	1065	
Ala	Cys	Lys	Lys	His	Glu	Leu	Tyr	Val	Ser	Phe		
		330				335						
CGA	GAC	CTG	GGC	TGG	CAG	GAC	TGG	ATC	ATC	GCG	1098	
Arg	Asp	Leu	Gly	Trp	Gln	Asp	Trp	Ile	Ile	Ala		
340					345					350		
CCT	GAA	GGC	TAC	GCC	GCC	TAC	TAC	TGT	GAG	GGG	1131	
Pro	Glu	Gly	Tyr	Ala	Ala	Tyr	Tyr	Cys	Glu	Gly		
				355						360		
GAG	TGT	GCC	TTC	CCT	CTG	AAC	TCC	TAC	ATG	AAC	1164	
Glu	Cys	Ala	Phe	Pro	Leu	Asn	Ser	Tyr	Met	Asn		
			365						370			
GCC	ACC	AAC	CAC	GCC	ATC	GTG	CAG	ACG	CTG	GTC	1197	
Ala	Thr	Asn	His	Ala	Ile	Val	Gln	Thr	Leu	Val		
		375					380					
CAC	TTC	ATC	AAC	CCG	GAA	ACG	GTG	CCC	AAG	CCC	1230	
His	Phe	Ile	Asn	Pro	Glu	Thr	Val	Pro	Lys	Pro		
		385				390						
TGC	TGT	GCG	CCC	ACG	CAG	CTC	AAT	GCC	ATC	TCC	1263	
Cys	Cys	Ala	Pro	Thr	Gln	Leu	Asn	Ala	Ile	Ser		
395					400					405		
GTC	CTC	TAC	TTC	GAT	GAC	AGC	TCC	AAC	GTC	ATC	1296	
Val	Leu	Tyr	Phe	Asp	Asp	Ser	Ser	Asn	Val	Ile		
				410						415		
CTG	AAG	AAA	TAC	AGA	AAC	ATG	GTG	GTC	CGG	GCC	1329	
Leu	Lys	Lys	Tyr	Arg	Asn	Met	Val	Val	Arg	Ala		
			420						425			
TGT	GGC	TGC	CAC	TAG	CTC	TCC	GAGA	ATT	CAG		1361	
Cys	Gly	Cys	His									
			430									
ACC	CTT	TGG	GGG	GCCA	AGT	TTT	TCT	GGAT	CCT	CCATT	GCTCG	1401

CCTTGGCCAG GAACCAGCAG ACCAACTGCC TTTGTGAGA 1441
CCTTCCCCTC CCTATCCCCA ACTTTAAAGG TGTGAGAGTA 1481
TTAGGAAACA TGAGCAGCAT ATGGCTTTTG ATCAGTTTTT 1521
CAGTGGCAGC ATCCAATGAA CAAGATCCTA CAAGCTGTGC 1561
AGGCAAAACC TAGCAGGAAA AAAAAACAAC GCATAAAGAA 1601
AAATGGCCGG GCCAGGTCAT TGGCTGGGAA GTCTCAGCCA 1641
TGCACGGACT CGTTTCCAGA GGTAATTATG AGCGCCTACC 1681
AGCCAGGCCA CCCAGCCGTG GGAGGAAGGG GGC GTGGCAA 1721
GGGGTGGGCA CATGGGTGTC TGTGCGAAAG GAAAATTGAC 1761
CCGGAAGTTC CTGTAATAAA TGTCACAATA AAACGAATGA 1801
ATGAAAAAAA AAAAAAAAAA A 1822

What is claimed is:

1. An osteogenic device for implantation in a mammal, the device comprising:
- a biocompatible, in vivo biodegradable matrix of mineral-free, delipidated Type I insoluble bone collagen particles, depleted in noncollagenous protein; and
- a protein produced by the expression of recombinant DNA in a mammalian host cell, the protein comprising two oxidized subunits, the amino acid sequence of each subunit being sufficiently duplicative of the amino sequence (Seq. ID No.6):

OP1-16V

[illegible]

such that the dimeric species comprising said subunits has a conformation that is capable of inducing endochondral bone formation in a mammal when disposed within said matrix and implanted in said mammal.

2. An osteogenic protein expressed from recombinant DNA in a mammalian host cell and capable of inducing endochondral bone formation in a mammal when disposed within a matrix implanted in said mammal;

a protein produced by the expression of recombinant DNA in a mammalian host cell, the protein comprising two oxidized subunits, the amino acid sequence of each subunit being sufficiently duplicative of the amino sequence (Seq. ID No.6):

QP1-16V

[illegible]

3. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit has at least 70% homology with the amino acid sequence (Seq. ID No.6):

OP1-16V

```

                                     30
                                     V A E N S
                                     40
S S D Q R Q A C K K H E L Y V
      50
S F R D L G W Q D W I I A P E
      60
      70
G Y A A Y Y C E G E C A F P L
      80
N S Y M N A T N H A I V Q T L
      90
      100
V H F I N P E T V P K P C C A
      110
P T Q L N A I S V L Y F D D S
      120
      130
S N V I L K K Y R N M V V R A
C G C H.

```

4. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit has at least 80% homology with the amino acid sequence (Seq. ID No.6):

OP1-16V

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                                     30
                                     V A E N S
                                     40
S S D Q R Q A C K K H E L Y V
      50
S F R D L G W Q D W I I A P E
      60
      70
G Y A A Y Y C E G E C A F P L

```

80
 N S Y M N A T N H A I V Q T L 90
 100
 V H F I N P E T V P K P C C A
 110 120
 P T Q L N A I S V L Y F D D S
 130
 S N V I L K K Y R N M V V R A
 C G C H.

5. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit comprises (Seq. ID No. 6):

QPI-16V

30
 V A E N S
 40
 S S D Q R Q A C K K H E L Y V
 50 60
 S F R D L G W Q D W I I A P E
 70
 G Y A A Y Y C E G E C A F P L
 80 90
 N S Y M N A T N H A I V Q T L
 100
 V H F I N P E T V P K P C C A
 110 120
 P T Q L N A I S V L Y F D D S
 130
 S N V I L K K Y R N M V V R A
 C G C H.

6. The invention of claim 1 or 2 wherein the amino acid sequence of said subunit comprises (Seq. ID No. 1):

OPI-18

```

1      10
S T G S K Q R S Q N R S K T P
      20
K N Q E A L R M A N V A E N S
      40
S S D Q R Q A C K K H E L Y V
      50
S F R D L G W Q D W I I A P E
      60
G Y A A Y Y C E G E C A F P L
      70
N S Y M N A T N H A I V Q T L
      80
V H F I N P E T V P K P C C A
      90
P T Q L N A I S V L Y F D D S
      100
S N V I L K K Y R N M V V R A
      110
C G C H.

```

7. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit comprises (Seq. ID No. 2):

OPI-16S

```

      8      10
      S Q N R S K T P
      20
K N Q E A L R M A N V A E N S
      40
S S D Q R Q A C K K H E L Y V
      50
S F R D L G W Q D W I I A P E
      60
G Y A A Y Y C E G E C A F P L
      70
N S Y M N A T N H A I V Q T L
      80
V H F I N P E T V P K P C C A
      90
P T Q L N A I S V L Y F D D S
      100
S N V I L K K Y R N M V V R A
      110
C G C H.

```

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8. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit comprises (Seq. ID No. 3):

OPl-16L

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                21                                30
                L R M A N V A E N S
                40
S S D Q R Q A C K K H E L Y V
                50                                60
S F R D L G W Q D W I I A P E
                70
G Y A A Y Y C E G E C A F P L
                80                                90
N S Y M N A T N H A I V Q T L
                100
V H F I N P E T V P K P C C A
                110                                120
P T Q L N A I S V L Y F D D S
                130
S N V I L K K Y R N M V V R A
C G C H.

```

9. The invention of claim 1 or 2 wherein the amino acid sequence of each of said subunit comprises (Seq. ID No. 4):

OPl-16M

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                23                                30
                M A N V A E N S
                40
S S D Q R Q A C K K H E L Y V
                50                                60
S F R D L G W Q D W I I A P E
                70
G Y A A Y Y C E G E C A F P L
                80                                90
N S Y M N A T N H A I V Q T L
                100
V H F I N P E T V P K P C C A

```

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      10      20      30      40      50
GGTGGCGGGCCCGGAGCCCGGAGCCCGGGTAGCGCGTAGAGCCGGCGCGATGCACGTGC
                               SmaI                               M H V
      70      80      90      100     110     1
TCACTGCGAGCTGCGGCGCCGCACAGCTTCGTGGCGCTCTGGGCACCCCTGTTCTCTGC
S L R A A A P H S F V A L W A P L F L
      130     140     150     160     170     1
CGCTCCGCCCTGGCCGACTTCAGCCTGGACAACGAGGTGCACTCGAGCTTCATCTACC
R S A L A D F S L D N E V H S S F I H

      190     200     210     220     230     2
CGCCTCCGCAGCCAGGAGCGGCGGGAGATGCAGCGCGAGATCCTCTCCATTTTGGGCT
R L R S Q E R R E M Q R E I L S I L G
      250     260     270     280     290     3
CCCCACCGCCCGCGCCCGCACCTCCAGGGCAAGCACAACCTCGGCACCCATGTTTCATGC
P H R P R P H L Q G K H N S A P M F M
      310     320     330     340     350     3
GACCTGTACAACGCCATGGCGGTGGAGGAGGGCGGCGGGCCCGGCGGCCAGGGCTTCT
D L Y N A M A V E E G G G P G G Q G F
      370     380     390     400     410     4
TACCCCTACAAGGCCGTCTTCAGTACCCAGGGCCCCCTCTGGCCAGCCTGCAAGATA
Y P Y K A V F S T Q G P P L A S L Q D
      430     440     450     460     470     4
CATTTCTCACCGACGCCGACATGGTCATGAGCTTCGTCAACCTCGTGGAACATGACA
H F L T D A D M V M S F V N L V E H D
      490     500     510     520     530     5
GAATTCTTCCACCCACGCTACCACCATCGAGAGTTCCGGTTTGATCTTTCCAAGATCC
E F F H P R Y H H R E F R F D L S K I
      550     560     570     580     590     6
GAAGGGGAAGCTGTCACGGCAGCCGAATTCCGGATCTACAAGGACTACATCCGGGAAC
E G E A V T A A E F R I Y K D Y I R E
      610     620     630     640     650     6
TTCGACAATGAGACGTTCCGGATCAGCGTTTATCAGGTGCTCCAGGAGCACTTGGGC
F D N E T F R I S V Y Q V L Q E H L G
      670     680     690     700     710     7
GAATCGGATCTCTTCTGCTCGACAGCCGTACCCTCTGGGCCTCGGAGGAGGGCTGGC
E S D L F L L D S R T L W A S E E G W
      730     740     750     760     770     7
GTGTTTGACATCACAGCCACCAGCAACCACTGGGTGGTCAATCCGCGGCACAACCTGC
V F D I T A T S N H W V V N P R H N L
      790     800     810     820     830     8
CTGCAGCTCTCGGTGGAGACGCTGGATGGGCAGAGCATCAACCCCAAGTTGGCGGGCC
L Q L S V E T L D G Q S I N P K L A G
      850     860     870     880     890     8
ATTGGGCGGCACGGGCCCCAGAACAAGCAGCCCTTCATGGTGGCTTTCTTCAAGGCC
I G R H G P Q N K Q P F M V A F F K A
      910     920     930     940     950     9
GAGGTCCACTTCCGCAGCATCCGGTCCACGGGGAGCAAACAGCGCAGCCAGAACCGCT
E V H F R S I R S T G S K Q R S Q N R
      970     980     990     1000    1010    10
AAGACGCCCAAGAACCAGGAAGCCCTGCGGATGGCCAACGTGGCAGAGAACAGCAGCA
K T P K N Q E A L R M A N V A E N S S
      1030    1040    1050    1060    1070    108

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FIG. 2-1

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GACCAGAGGCAGGCCTGTAAGAAGCACGAGCTGTATGTCAGCTTCCGAGACCTGGGCTGG
D Q R Q A C K K H E L Y V S F R D L G W
1090 1100 1110 1120 1130 1140
CAGGACTGGATCATCGCGCCTGAAGGCTACGCCGCTACTACTGTGAGGGGGAGTGTGCC
Q D W I I A P E G Y A A Y Y C E G E C A
1150 1160 1170 1180 1190 1200
TTCCCTCTGAACTCCTACATGAACGCCACCAACCACGCCATCGTGCAGACGCTGGTCCAC
F P L N S Y M N A T N H A I V Q T L V H
1210 1220 1230 1240 1250 1260
TTCATCAACCCGGAACGGTGCCCAAGCCCTGCTGTGCGCCACGCAGCTCAATGCCATC
F I N P E T V P K P C C A P T Q L N A I
1270 1280 1290 1300 1310 1320
TCCGTCCTCTACTTCGATGACAGCTCCAACGTCATCCTGAAGAAATACAGAAACATGGTG
S V L Y F D D S S N V I L K K Y R N M V
1330 1340 1350 1360 1370 1380
GTCCGGGCCTGTGGCTGCCACTAGCTCCTCCGAGAATTCAGACCCTTTGGGGCCAAGTTT
V R A C G C H *
1390 1400 1410 1420 1430 1440
TTCTGGATCCTCCATTGCTCGCCTTGGCCAGGAACCAGCAGACCAACTGCCTTTTGTGAG
BamH1
1450 1460 1470 1480 1490 1500
ACCTTCCCCTCCCTATCCCCAACTTTAAAGGTGTGAGAGTATTAGGAAACATGAGCAGCA
1510 1520 1530 1540 1550 1560
TATGGCTTTTGTATCAGTTTTTTCAGTGGCAGCATCCAATGAACAAGATCCTACAAGCTGTG
1570 1580 1590 1600 1610 1620
CAGGCAAAACCTAGCAGGAAAAAAAAAACAACGCATAAAGAAAAATGGCCGGGCCAGGTCA
1630 1640 1650 1660 1670 1680
TTGGCTGGGAAGTCTCAGCCATGCACGGACTCGTTTCCAGAGGTAATTATGAGCGCCTAC
1690 1700 1710 1720 1730 1740
CAGCCAGGCCACCCAGCCGTGGGAGGAAGGGGGCGTGGCAAGGGGTGGGCACATTGGTGT
1750 1760 1770 1780 1790 1800
CTGTGCGAAAGGAAAATTGACCCGGAAGTTCCTGTAATAAATGTCACAATAAAACGAATG
1810 1820
AATGAAAAAAAAAAAAAAAAAAAA

FIG. 2-2

110 120
P T Q L N A I S V L Y F D D S
S N V I L K K Y R N M V V R A
C G C H.

10. The invention of claim 1 or 2 wherein the amino acid sequence of each of said subunit comprises (Seq. ID No. 5):

OPI-16A

24 30
A N V A E N S
40
S S D Q R Q A C K K H E L Y V
50 60
S F R D L G W Q D W I I A P E
70
G Y A A Y Y C E G E C A F P L
80 90
N S Y M N A T N H A I V Q T L
100
V H F I N P E T V P K P C C A
110 120
P T Q L N A I S V L Y F D D S
130
S N V I L K K Y R N M V V R A
C G C H.

11. The invention of claim 1 or 2 wherein said protein has an apparent molecular weight of about 30 kD when oxidized, as determined by comparison to molecular weight standards in SDS-polyacrylamide gel electrophoresis.

12. The invention of claim 1 or 2 wherein said protein has an apparent molecular weight of about 36 kD when oxidized, as determined by comparison to molecular weight standards in SDS-polyacrylamide gel electrophoresis.

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